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High Prevalence of HTLV-I Infection Among the Family Members of a Patient With Adult T-Cell Leukemia/Lymphoma From Northeastern Japan

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Human T-cell lymphotropic virus type I (HTLV-I) is transmitted through infected lymphocytes mostly by breast feeding. In the present study, high prevalence of HTLV-I infection was disclosed in the family members of a patient with adult T-cell leukemia/lymphoma (ATL), all of whom were residents of Iwate, northeastern Japan. Long-term follow-up is necessary for people with HTLV-I infection because of the risk of developing ATL after a certain period of latency. New inventive treatments for the acute and lymphomatous types of ATL are needed. Am. J. Hematol. 61:78–81, 1999. © 1999 Wiley-Liss, Inc.

Key words: adult T-cell leukemia/lymphoma; HTLV-I; family study

INTRODUCTION

Adult T-cell leukemia/lymphoma (ATL) is etiologically linked to the human T-cell lymphotropic virus type I (HTLV-I) infection [1]. HTLV-I, a retrovirus, is endemic in southern Japan (Kyushu islands) and the Caribbean basin and occurs sporadically in other parts of the world [2]. It is estimated that 1–2 million people are infected with HTLV-I in Japan and ATL develops in 600-700 seropositive individuals with the incidence of 0.1–0.2% (1 in 1,000–2,000 seropositive individuals) annually [3]. HTLV-I is transmitted through the infected T-lymphocytes by three routes: mother to child by breast feeding; male to female by sexual contact; and by blood transfusions [3]. Because of the mode of transmission of HTLV-I, the family members of a patient with ATL are considered to have a chance of infection with HTLV-I with significantly higher incidence.

In the present study, six siblings and three children of the patient with ATL were evaluated for HTLV-I infection.

CASE REPORT

The patient was a 55-year-old female and was born and grew up in Iwate prefecture located in northeastern Japan. The patient had been doing well until 1992, when she started complaining of heartburn and was diagnosed as having an esophageal candidiasis by a local physician. During the time between April 24 and May 21, 1997, the patient was admitted to a local hospital and was treated for pneumonia and esophageal candidiasis. Half a year later, the patient started having abdominal fullness, constipation, and vomiting. The patient was admitted to the Nagoya City Higashi General Hospital for disease work-up and management on December 26, 1997.

Physical examinations revealed bilateral axillary lymphadenopathies and hepatosplenomegaly. The patient was alert but drowsy. Her complete blood count was unremarkable with white blood cells of 4.9×10^9/l with normal differentials, hemoglobin 13.8 g/dl, and platelet 224×10^9/l. Her biochemistry was remarkable with an elevated LDH of 534 IU/l (normal, 150–390 IU/l) and an increased calcium level of 14.8 mg/dl (normal, 8.0–10.4 mg/dl). Her symptoms, drowsiness, constipation, and vomiting, were considered to be caused by the hypercalcemia. However, the possibility of hyperparathyroidism was denied by the following data: high sensitivity parathyroid hormone (HS-PTH) was 310 pg/ml (normal, 160–520 pg/ml); C-terminal PTH was 0.2 ng/ml (normal,

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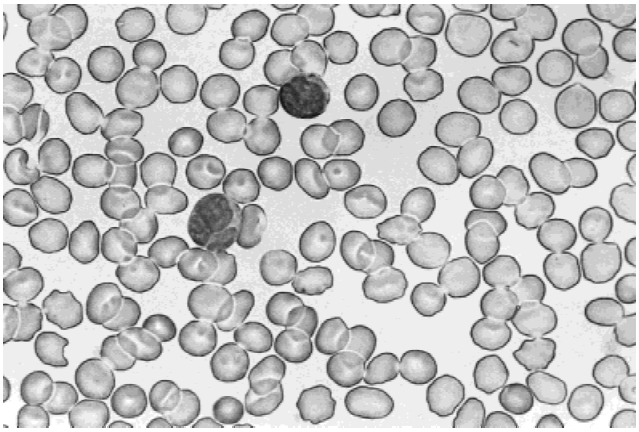

Fig. 1. Atypical lymphocytes with convoluted nuclei in the peripheral blood (oil immersion).

less than 0.5 ng/ml); intact PTH was 7 pg/ml (normal, 10–65 pg/ml); and urine cyclic AMP was 0.87 μmol/day (normal, 1.8–6.3 μmol/day). PTH related protein (PTHrP) was slightly elevated to 2.0 pmol/l (normal, less than 0.6 pmol/l). The results of thyroid function tests were interpreted as suggesting a euthyroid sick syndrome [4] because free T3 was 0.1 ng/ml (normal, 2.47–4.34 ng/ml), free T4 was 0.57 ng/dl (normal, 0.97–1.79 ng/dl), and TSH was 2.7 μU/ml (normal, 0.34–3.5 μU/ml). Whole-body computed tomography scan was performed and revealed multiple paraaortic lymphadenopathy, hepatosplenomegaly, and a low density area in the liver. Based on the knowledge of hypercalcemia associated with hematologic malignancies, her peripheral blood films were reviewed and atypical lymphocytes with convoluted nuclei as depicted in Figure 1 were detected. Her bone marrow was normocellular with a focal proliferation of atypical small lymphocytes with convoluted nuclei. Serum and urine electrophoresis didn't reveal any monoclonal spike. Antibody against HTLV-I was detected and the patient was diagnosed as having ATL. The patient had a systemic skin rash that was biopsied and diagnosed as cutaneous involvement by ATL.

Chemotherapy composed of cyclophosphamide, doxorubicin, vincristine, and prednisolone was instituted along with the treatment for hypercalcemia with bisphosphonate. However, the patient showed a progressive deterioration and died on January 31, 1998.

Her family history was remarkable for high prevalence of hematologic malignancies; the patient's mother died of malignant lymphoma at the age of 66 years, and all of the patient's mother's siblings died of leukemia in the hospitals of Iwate prefecture—a sister and the only brother died of leukemia of unknown lineage in 1994 and in May 1997, respectively, and another sister died of ATL in February 1997, as depicted in Figure 2.

METHODS

The patient had seven siblings and three children. Blood samples were drawn after obtaining consent from six siblings and all three children and were shipped to the Special Reference Laboratory, Tokyo, Japan, to be subjected to the evaluation of antibody to HTLV-I by passive agglutination method.

RESULTS

The results of serological study for HTLV-I are shown in the pedigree depicted in Figure 2. Three siblings out of six studied had antibody to HTLV-I; so did the daughter of the patient.

DISCUSSION

ATL is classified into four clinical subtypes: acute; lymphomatous; chronic; and smoldering types, based on the number of abnormal convoluted lymphocytes in peripheral blood, serum LDH level, tumor lesions in various organs, and clinical course [3]. Because the patient did not have lymphocytosis of more than 4,000/μl with atypical lymphocytes of more than 1%, and because her axillary and paraaortic lymphadenopathies were compatible with the clinical features of lymphoma, the patient was identified as belonging to the lymphomatous type [5].

Major complications of ATL are hypercalcemia and serious infections by bacteria, fungi, protozoa, and viruses. Hypercalcemia is found in about 20–30% of patients with ATL, mostly of acute and lymphomatous types, and is considered to be in the category of a humoral hypercalcemia of malignancy, which is found in association with some solid tumors [6,7]. The causative humoral factor known as parathyroid hormone-related protein (PTHrP) [8] has been found in HTLV-I–infected T-cell lines and in fresh ATL leukemic cells [9,10]. Our patient was also noted to have an elevated level of PTHrP without the evidence of hyperparathyroidism.

Patients with ATL are known to have a cellular immune deficiency, which allows opportunistic infections to develop [11]. The patient had esophageal candidiasis 5 years and pneumonia 6 months before the diagnosis of ATL, respectively. These episodes seem to support the idea that the patient was already in a state of immune deficiency at least 5 years previous to diagnosis.

Various regimens of cytotoxic chemotherapy have been used to treat patients with the acute and lymphomatous types of ATL, but the rates of complete response are below 30% and the responses lack durability [11]. Thus, the prognosis of acute and lymphomatous types of ATL is very poor with median survival for acute type of

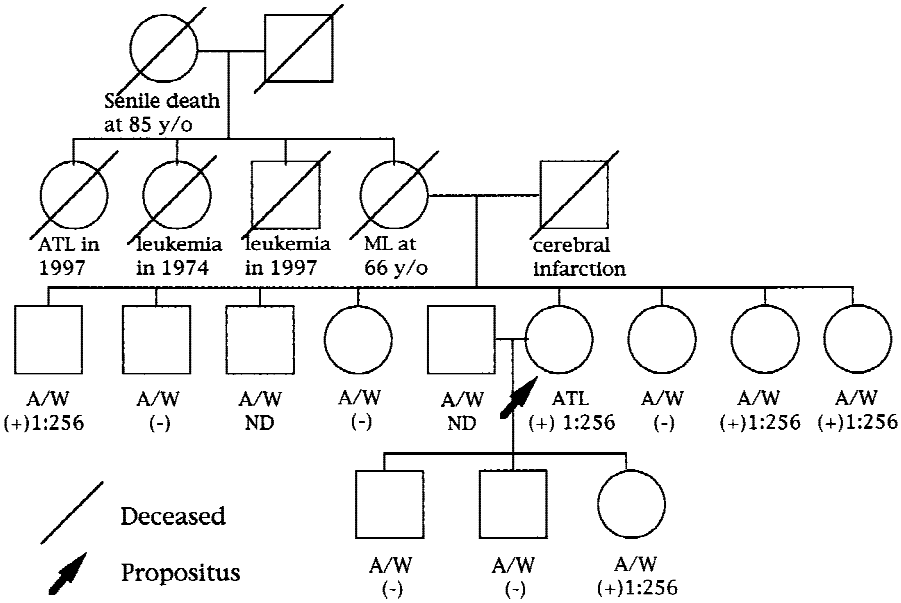

Fig. 2. Genogram of the distribution of hematologic malignancies and HTLV-I infection in the patient's family. ATL, adult T-cell leukemia/lymphoma; ML, malignant lymphoma; A/W, alive and well; ND, not tested.

6.2 months and for lymphomatous type of 10.2 months [3]. Among the poor prognostic features associated with the acute and lymphomatous types are hypercalcemia, elevated serum LDH, poor performance status, age over 40 years, and multiple sites of disease [11], all of which were identified in this patient. New treatments are thus badly needed for the acute and lymphomatous types of ATL. It is noteworthy that Gill et al. [2] reported a favorable response in patients with ATL treated with zidovudine and interferon alfa.

ATL occurs in less than 5% of people with HTLV-I infection, with an average latency period of more than 30 years [12]. The mean age of onset of ATL is 55 years, and the ratio of male to female patients is 1.4 to 2 [13]. In the present study, sera were obtained from six females, including the patient, and from four males. Four females out of six (66.7%) and only one male out of four (25%) had HTLV-I infection, implicating female preponderance in HTLV-I infection. Although the present study revealed a high prevalence of HTLV-I infection in the family members of a patient with ATL, the method used was an evaluation of antibody to HTLV-I by passive agglutination. If the antibody to HTLV-I had been evaluated by a more sensitive method such as Western blotting, or further, proviral DNA of HTLV-I had been evaluated by Southern blot hybridization or PCR method in the lymphocytes of the family members, even a higher prevalence of HTLV-I infection could have been disclosed. Another characteristic in the patient's family was that the patient's mother died of malignant lymphoma at the age of 66 years and her three siblings died of leukemia, including ATL. Although no further clinical information was obtained, it is highly probable that all four of these people had ATL of different subtypes and that the patient's grandmother, who died of senility at the age of 85 years, was an HTLV-I carrier. According to the family members, the patient's family members have been residents of Iwate prefecture for a long time and had no relation with Kyushu island. Although HTLV-I infection has been known to be endemic in Kyushu island of Japan, geographical study disclosed endemic areas spreading all over Japan, Okinawa islands, and areas facing the Pacific Ocean of Shikoku island, Key pennisula, and northeastern Japan including Iwate prefecture [13].

Since the mode of transmission of HTLV-I was clarified, breast feeding for more than 6 months by mothers with HTLV-I antibody is not recommended in Japan.

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